

## Leishmanicidal compounds of natural origin: their prospective mantle in antileishmanial therapy

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Leishmaniasis is a complex vector-borne protozoan disease caused by parasites of the genus *Leishmania*. The parasites hugely vary in their mode of tropism giving rise to different non-lethal to fatal clinical patterns of the disease. Afflicting millions, the disease is endemic in tropics and sub-tropics, where majority of the affected individuals are rural and unsound economically, leading to its classification as one of the neglected tropical diseases, which is, however, contradicted by its alliance with AIDS and spread to non-endemic countries. With no antileishmanial vaccine in hand and available chemotherapy being fallacious, drug development from alternate natural resources against this relentless disease is viewed upon as an exemplary approach. Herein, we have put together, a concise description of the disease, lacunae in the present therapy and promising antileishmanial leads of natural origin in the past decade.

**Keywords:** Leishmaniasis; *Leishmania*; antileishmanial; leishmanicidal; natural products; secondary metabolites

### 1. Leishmaniasis: outlook of the syndrome

Leishmaniasis is a vector borne affliction defeated only by malaria in terms of mortality associated with parasitic diseases. More than 21 leishmanial species are associated with the complex syndrome that is transmitted by at least 30 distinct species of *Phlebotomine* arthropods. The *Leishmania* parasites are digenetic (extracellular promastigote and intracellular amastigote forms), homing inside macrophages and the disease varies in its clinical spectrum depending upon the invading species. The clinical symptoms of leishmaniasis are diverse, extending from non-fatal skin lesions (cutaneous leishmaniasis, CL) to potentially fatal mucocutaneous leishmaniasis (MCL) and lethal visceral infections (visceral leishmaniasis, VL) [1]. CL is the most common in countries like Afghanistan, Saudi Arabia, Peru, Brazil, Iran and Syria where 0.7 million cases are reported annually. Though non-fatal, CL infections can result in life-long persisting disfiguring scars or may lead to relapse in the form of MCL [2]. MCL develops as ulcerative disease of nasal cartilaginous system and may become fatal with time when it disseminates from oro-pharyngeal region to upper respiratory tract rendering the host susceptible to secondary infections [1]. Most of the MCL cases are concentrated in South America, Brazil, Peru and Bolivia. VL, is the lethal manifestation of the disease in which parasites specifically target the host's liver, spleen, bone marrow and lymph nodes where their uncontrolled propagation in the absence of any treatment leads to death [3]. Much of the VL burden (~90%) is shared by India, Bangladesh, Nepal, South Sudan, Sudan and Brazil from where 0.2 to 0.4 million cases are reported on annual basis [4]. The mortality associated with VL amounts to 60, 000 deaths each year but is expected to be higher under the shadow of false diagnosis and misreporting. The complications associated with VL are further exacerbated with its relapse in the form of post kala-azar dermal leishmaniasis (PKDL) and co-infection with human immunodeficiency virus (HIV). PKDL progresses as macular, papular and nodular skin lesions, which harbour acute parasitic load serving as putative reservoirs in between epidemic outbreaks [5]. The association between acquired immunodeficiency syndrome (AIDS) and VL is worrisome as it has led to expansion of VL, well outside its endemic foci [6].

### 2. Leishmaniasis: disease pathogenesis

*Leishmania* parasites are peculiar with 'macrophages' as a choice for their host cells. Macrophages constitute prime sentinels of innate immune response, in other words, *Leishmania* parasites clearly vanquish cell-mediated immunity (CMI) to establish grave parasitism. *Leishmania* are notorious parasites, which mastermind their survival in host macrophages by adopting multifarious strategies. A detailed outlook of complex immunopathogenesis of leishmaniasis is beyond the ambit of this space, however several facets are covered in detail by many authors including us previously [7-9], and the key aspects are concisely summarized in following section.

In brief, upon entering the host, *Leishmania* parasites attempt to gain neutrophil-dependent [10] or independent [9 and references therein] entry into the host macrophages. Once inside the macrophages, *Leishmania* promastigotes survive and transform into amastigote form inside the phagolysosomal vacuoles, a process for which hosts are levied a hefty fee as many of their microbicidal functions and cell signalling pathways are downmodulated or impaired to favour *Leishmania* survival.

*Leishmania* promastigotes home inside the phagosomes where they retard phagosome maturation, and defer the process of phagosome-endosome/lysosome fusion, which leads to the formation of phagolysosomal compartments. *Leishmania* surface lipophosphoglycan (LPG) retards phagosome maturation [11], alters its biophysical properties thereby rendering it less fusogenic [12] and deters phagosome acidification [13]. All these events maintain a favorable environment for promastigotes survival and transformation into amastigote stage.

*Leishmania* parasites have evolved multilayered host-silencing strategies ranging from amendment of host metabolic pathways, interference with host cell-signalling and translation, inhibition of reactive-nitrogen (RNI) and -oxygen (ROI) intermediates and annihilation of antigen presentation to delay in induction of apoptosis in infected macrophages. *Leishmania* elongation factor (EF)-1 $\alpha$  is known to bind and activate Src homology-2 domain containing PTP (protein tyrosine phosphatase) SHP-1 [14] which exerts negative effect on Janus kinase/ signal transducer and activator of transcription (JAK/STAT), mitogen-activated protein-kinase (MAPK) and interleukin (IL)-1 receptor associated kinase-1 (IRAK-1) leading to down modulation of innate immune responses and specific blockage of pro-inflammatory cytokines, nitric oxide (NO) production and c-FOS expression [15-16]. *Leishmania* surface protease GP63 and fructose-1,6-biphosphate aldolase are also known to participate in SHP-1 activation [15,17].

*Leishmania* LPG also hampers protein kinase C (PKC) mediated signalling, which is pivotal for its survival. *Leishmania* impairs calcium (Ca<sup>2+</sup>) dependent classical PKC (c-PKC) activation, which is also aided by LPG [18]. PKC mediated signalling events are vital for activation of many macrophage microbicidal functions such as induction of respiratory burst and c-FOS expression; also impaired PKC mediated signalling renders macrophages unresponsive to activation by extracellular cytokines such as interferon (INF)- $\gamma$  and tumour necrosis factor (TNF)- $\alpha$  [18 and references therein]. Calcium homeostasis is disturbed during *Leishmania* infection with elevation of intracellular Ca<sup>2+</sup> [19]. Ca<sup>2+</sup> acts as secondary messenger that steers various cellular events including activation of c-PKCs and modulation of T helper type (Th)-1/Th2 cytokines.

Innate immune responses are also down regulated by activation of suppressor of cytokine signalling (SOCS) gene in human macrophages by *L. donovani* to curb cytokine production [20] and by enhancement of intracellular ceramide levels in BALB/c mice macrophages. Elevated intracellular ceramide downregulates c-PKCs activation, which further leads to inhibition of activated protein-1 (AP-1) and nuclear factor (NF)- $\kappa$ B. Both AP-1 and NF- $\kappa$ B are salient transcription factors involved in initiation of pro-inflammatory immune response [21]. *Leishmania* GP63 has also been demonstrated to preferentially target AP-1 subunits within the nuclear membrane. Recently, Isnard et al. [22] have demonstrated that GP63 can affect host nucleoporins, nucleoskeleton, and modulate the nuclear-cytoplasmic transport via inducing cleavage.

Host translation also gets swayed by *Leishmania* parasites. GP63 cleaves mechanistic target of rapamycin (mTOR), a serine/threonine kinase known to play a predominant role in initiation of innate immunity [23]. *Leishmania* parasites thwart the generation of RNS and ROI or reactive oxygen species (ROS). Since, NO production is essential for parasite elimination, *Leishmania* suppresses the production of Th1 cytokines, which in turn leads to failure of induction of nitric oxide synthase II (NOS II), the enzyme responsible for NO generation [24]. Other glycoinositol phospholipids (GIPLs) present on parasite surface also suppress NO production [25]. ROS generation is reported to inhibit the activation of PTPs leading to MAPK activation and induction of pro-inflammatory immune response, which suggest indirect and cardinal role of ROS in control of *Leishmania* infection [26]. *Leishmania* parasites put forward a bifurcated defence policy to quash ROIs. ROS are either scavenged directly by LPG and GP63 [27] or their production is inhibited by averting the assembly of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex [28-29,7]. Basu Ball et al. [26] demonstrated that ROS production in *L. donovani* parasites is negatively regulated by uncoupling protein-2. *Leishmania* parasites yet again employ species-specific different mechanisms to either suppress/decimate major histocompatibility complex (MHC) mediated antigen presentation. *L. amazonensis* promastigotes internalize and degrade host MHC molecules [30] whereas *L. major* disturbs the intracellular loading of MHC class II molecules with antigenic peptides [31] and *L. donovani* inhibits MHC class II production at transcriptional level in cAMP independent manner [32]. *Leishmania* parasites also delay apoptosis in infected macrophages by preventing cytochrome c release from mitochondria or by activation of PI3/Akt signalling. Activation of PI3K also leads to elevation of Th2 cytokine with concomitant suppression of pro-inflammatory cytokines [8].

### 3. Therapeutic approaches against leishmaniasis

Chemotherapy against leishmaniasis is antiquated and atrocious. Except for miltefosine, all other drugs such as antimonials (1<sup>st</sup> line of drugs), amphotericin B (AmB) (2<sup>nd</sup> line of drugs) and paromomycin require parenteral administration and continuous monitoring, which is a huge disadvantage for leishmaniasis afflicted poverty-stricken population. Cure is often associated with awful side effects and emerging drug resistance presents a grave issue, which has already led to abolition of use of antimonials from Bihar, India [33].

Despite decades of efforts, there is no licensed vaccine available against leishmaniasis. An effectual, cross-protective antileishmanial vaccine is available in theory, but in actual, it is a laborious task. Each *Leishmania* species is distinct with complex life cycles and intracellular location of these parasites coupled with a complex interplay of host immunity have severely impeded the prospects of commercially viable antileishmanial vaccine.

In the absence of vaccine, antileishmanial therapeutic approaches have hopped from single-drug formulations to combined therapy approach that despite its initial success was later on demonstrated to be prone to drug resistance [34].

#### 4. Rescuing diabolical antileishmanial chemotherapy: drug development from alternat resources

The abominable state of current antileishmanial drugs desperately seeks profound revival and given the limitations of synthetic chemistry, drug discovery from natural resources is now looked upon as vastly viable and beneficial option. This is also supported by factual data [35] and history of anti-parasitic drug discovery. Exploration of plants as a source of potent antiprotozoals led to the discovery of quinine [36] and artemisinin as potent anti-malarial drugs along with emetine, which was found to be amoebicidal in nature [37].

Since, the major chunk of population bearing leishmaniasis burden is rural, underprivileged and inhabit zones that are far out of reach of drug supply, the local population has learnt the use of plant preparations as antidote for leishmaniasis since ancient times. Several decades of cumulative research on anti-*Leishmania* drugs of plant-origin have not only yielded innumerable plant extracts/semi-purified fractions/ plant-derived secondary metabolites (as mentioned in Table 1) but have also simultaneously pushed the envelope further for discovery of potent leishmanicidal fractions/compounds from diverse natural resources including fungi, algae, invertebrates and some of the vertebrates (as listed in Table 2).

Many plant-derived secondary metabolites have exhibited target-specific activity against *Leishmania* parasites. Quercetin disrupts iron metabolism in *L. donovani* [38] and also *L. amazonensis* arginase along with Quercitrin [39], Fisetin and Luteolin [40]. Plumbagin is known to disrupt Trypanothione reductase (TryR) [41]. On the basis of molecular docking, several other TryR inhibitors have been identified such as taxifolin or dihydroquercetin, tomatine, solasodine amongst others [42-43]. Peganine hydrochloride dihydrate and niranthin have been shown to be *Leishmania* DNA topoisomerase I inhibitors and induce apoptosis in both stages of *L. donovani* [44-45]. Apoptosis is not only the preferred mode of cell-death but also the study of apoptotic pathways in *Leishmania* has divulged several key targets, which can be optimized for rapid antileishmanial drug development. Several other natural products like withanolides [46], citral [47], berberine [48], curcumin [49], artemisinin [50], withaferin A [51] and racemoside A [52] have displayed apoptosis inducing potential in leishmanial parasites.

**Table 1** Plant natural products with antileishmanial activity

Active Principle	Natural source	<i>Leishmania</i> spp.	Reference	Active Principle	Natural source	<i>Leishmania</i> spp.	Reference
5,3'-hydroxy-7,4'-dimethoxyflavone	<i>Picramnia</i> spp.	<i>L. panamensis</i>	[53]	Gallic acid Gallacocatechin Epigallocatechin	<i>Stryphnodendron obovatum</i>	<i>L. amazonensis</i>	[54]
31-norcyclolaudenone 24-methylene-cicloartanol β-Sitosterol Stigmasterol	<i>Musa paradisiaca</i>	<i>L. infantum</i>	[55]	12-methoxycarnosic acid	<i>Salvia repens</i>	<i>L. donovani</i>	[56]
Trixanolide	<i>Trixis antimenorrhoea</i>	<i>L. amazonensis</i> <i>L. braziliensis</i>	[57]	Casearins A, B, G & J	<i>Casearia sylvestris</i>	<i>L. infantum</i>	[58]
2-methyl-5-(3'-methyl-but-2'-enyloxy)-[1,4]-naphthoquinone	<i>Plumbago zeylanica</i>	<i>L. donovani</i>	[59]	Licarin A	<i>Aristolochia taliscana</i>	<i>L. major</i>	[60]
N-[7-(3',4'-methylenedioxyphenyl)-2(E),4(E)-heptadienoyl]pyrrolidine	<i>Piper amalago</i>	<i>L. amazonensis</i>	[61]	(E)-3,5,7,16-tetramethylheptadeca-2-en-1-ol (fatty alcohol)	<i>Terminalia arjuna</i>	<i>L. donovani</i>	[62]
Sambacaitaric acid 3-O-methyl-sambacaitaric acid 3-O-methyl-rosmarinic acid	<i>Hyptis pectinata</i>	<i>L. braziliensis</i>	[63]	Hydroxycopallic acid Methyl copalate Pinifolic acid Kaurenic acid	<i>Copaifera officinalis</i>	<i>L. amazonensis</i>	[64]
Eucalyptin Myrciaphenone A Quercetin derivatives Syringic acid Gallic acid derivatives	<i>Corymbia maculata</i>	<i>L. donovani</i>	[65]	Trans-β-caryophyllene	<i>Copaifera</i> spp.	<i>L. amazonensis</i>	[66]
Warifteine	<i>Cissampelos</i>	<i>L. chagasi</i>	[67]	Jacaranone	<i>Pentacalia</i>	<i>L. chagasi</i>	[68]

	<i>sympodialis</i>				<i>desiderabili-s</i>	<i>L. braziliensis</i> <i>L. amazonensis</i>	
Dillapiole	<i>Piper anduncum</i>	<i>L. amazonensis</i> <i>L. braziliensis</i>	[69]	Allicin	plants of family Alliaceae	<i>L. donovani</i> <i>L. infantum</i>	[70]
(-)-mammea A/BB	<i>Calophyllum brasiliense</i>	<i>L. major</i> <i>L. amazonensis</i>	[71-72]	Ramiflorines A & B	<i>Aspidosperma ramiflorum</i>	<i>L. amazonensis</i>	[73]
Sakuranetin	<i>Baccharis retusa</i>	various spp.	[74]	Polygodial	<i>Drimys brasiliensis</i>	<i>L. chagasi</i>	[75]
Caffeic acid Pectolarigenin	<i>Baccharis uncinella</i>	<i>L. amazonensis</i> <i>L. braziliensis</i>	[76]	Piperine	<i>Piper</i> spp.	<i>L. amazonensis</i>	[77]
O-methylarmepavine C37 trihydroxy bistetrahydrofuran Annoacinone Corosolone	<i>Annona muricata</i>	<i>L. chagasi</i>	[78]	Plumericin Isoplumericin	<i>Plumeria bicolor</i>	<i>L. donovani</i>	[79]
Thiophene derivatives	<i>Porophyllum ruderale</i>	<i>L. amazonensis</i>	[80]	Lupane	<i>Combretum leprosum</i>	<i>L. amazonensis</i>	[81]
7-Epiclusianone Garciniaphenone Guttiferone	<i>Garcinia brasiliensis</i>	<i>L. amazonensis</i>	[82]	$\gamma$ -Fagarine 3-(1'-dimethylallyl)-decursinol (-)-Heliettine	<i>Helietta apiculata</i>	<i>L. amazonensis</i>	[83]
(3S)-16,17-didehydrofalcarinol	<i>Tridax procumbens</i>	<i>L. mexicana</i>	[84]	Julocrotine	<i>Croton pullei</i> var <i>glabrior</i>	<i>L. amazonensis</i>	[85]
Dasyscyphin C	<i>Eclipta prostrata</i>	<i>L. major</i>	[86]	Piperovatine Piperlongumene	<i>Piper ovatum</i>	<i>L. amazonensis</i>	[87]
Limonene	<i>Citrus</i> spp.	Various spp.	[88]	LLD-3	<i>Lophanthera lactescens</i>	<i>L. amazonensis</i>	[89]
Piceatannol	<i>Euphorbia lagascae</i>	<i>L. donovani</i>	[90]	Castalagin	<i>Anogeisus leiocarpus</i>	different spp.	[91]
Machilin –G Veraguensin	<i>Nectandra megapotamica</i>	<i>L. donovani</i>	[92]	Psilostachyin Peruvine	<i>Ambrosia tenuifolia</i>	<i>L. mexicana</i>	[93]
Cubebin Piplartine	<i>Piper cubeba</i> <i>Piper retrofractum</i>	<i>L. donovani</i>	[94]	Resveratrol	<i>Vitis</i> spp.	<i>L. major</i>	[95]
Plumericin	<i>Himatanthus sucuba</i>	<i>L. amazonensis</i>	[96]	Malabaricones A&B	<i>Myristica malabarica</i>	<i>L. tropica</i>	[97]
Umbelliprenin Auraptene	<i>Ferula szowitsiana</i>	<i>L. major</i>	[98]	Cicerfuran	<i>Cicer bijugum</i>	<i>L. aethiopica</i>	[99]
(+)- Isodomesticine (+)- Norisodomesticine (+)- Nantenine (+)- Neolitsine	<i>Guatteria dumetorium</i>	<i>L. mexicana</i>	[100]	Nerolidol	wide spread occurrence	different spp.	[101]
Maesabalides I-VI	<i>Maesa balansae</i>	<i>L. infantum</i>	[102]	Parthenolide	<i>Tanacetum parthenium</i>	<i>L. amazonensis</i>	[103]

One of the chief objectives in developing pipeline antileishmanial drugs from natural resources is to identify substances that are high on specificity and low in toxicity. Insufficient bioavailability and poor solubility are other drawbacks associated with natural compounds. To overcome the aforementioned lacunae, multidirectional approaches such as preparation of synthetic derivatives, nano and liposomal formulations and their evaluation for antileishmanial activity is in vogue. A huge repertoire of synthetic antileishmanial compounds has been derived from natural compounds that have been described elsewhere [104,35]. Artemisinin-loaded nanoparticles [105] as well as nano-formulated curcumin and piperine have been evaluated in experimental VL [106-107]. Liposomal formulation of lupane

as well as turmerone-rich fractions from *Curcuma longa* have been evaluated against *L. amazonensis* [108-109]. The encouraging results obtained from these studies further highlight the colossal worth held by natural products in field of antiprotozoal therapy.

**Table 2** Natural products from alternate sources with leishmanicidal activity

Source	Active fraction/compound	<i>Leishmania</i> spp.	Reference	Source	Active fraction/compound	<i>Leishmania</i> spp.	Reference
<b>Algae</b>							
<i>Osmundaria obtusiloba</i>	EtOAc and EtOH	<i>L. amazonensis</i>	[110]	<i>Lessonia vadosa</i>	Fucosterol	<i>L. amazonensis</i> <i>L. infantum</i>	[111]
<i>Styopodium zonale</i> <i>Dictyota menstrualis</i> <i>Dictyota ciliolata</i>	EtOAc and hexane Pachydictyol A & Isopachydictyol A EtOAc and hexane						
<i>Chondrococcus hornemanni</i>	n-butanol	<i>L. donovani</i>	[112]	<i>Dictyota pfaffii</i>	Dolabelladi-enetriol	<i>L. amazonensis</i>	[113]
<i>Caulerpa sertularioides</i> <i>Garlicilaria corticata</i> <i>Garlicilaria salicornia</i> <i>Sargassum oligocystum</i>	Hot water extracts	<i>L. major</i>	[114]	<i>Canistrocarpus cervicornis</i>	4-Acetoxydolastane diterpene	<i>L. amazonensis</i>	[115]
<i>Laurencia dendroidea</i>	(-)-Elatol Obtusol	<i>L. amazonensis</i>	[116]	<i>Bostrychia tenella</i>	n-hexane and DCM	<i>L. amazonensis</i>	[117]
<b>Fungi</b>							
<i>Aspergillus</i> spp.	Kojic acid	<i>L. amazonensis</i>	[118]	<i>Fusarium</i> sp. TA54	Acetonitrile	<i>L. mexicana</i>	[119]
<i>Eurotium repens</i>	Echinulin & other phenol derivatives	<i>L. donovani</i>	[120]				
<b>Invertebrates</b>							
<i>Neofibularia nolitangere</i>	methylene chloride	<i>L. donovani</i>	[121]	Bulgaria propolis	Solvent extracts	various spp.	[122]
<i>Actinopyga lecanora</i>	n-butanol Holothurin B	<i>L. donovani</i>	[123]	Adana propolis	ethanolic extract	<i>L. tropica</i>	[124]
<i>Haliclona exigua</i>	n-butanol and methanol	<i>L. donovani</i>	[125]				
<b>Vertebrates</b>							
<i>Phyllomedusa oreades</i> <i>Phyllomedusa hypochondrialis</i> (frogs)	Dermaseptin 01	<i>L. amazonensis</i> <i>L. chagasi</i> <i>L. infantum</i>	[126]	<i>Siphonops annulatus</i> (limbless amphibia)	Skin secretion	<i>L. infantum</i>	[127]
<i>Phyllomedusa nordestina</i> (frog)	Phylloseptin 7	<i>L. infantum</i>	[128]	<i>Acanthopri-mnoa cristata</i> (cnidarian)	Cristaxenicin A	<i>L. amazonensis</i>	[129]
<i>Trimorphodon biscutatus lamda</i> (snake)	Trimorphin	<i>L. major</i>	[130]				

EtOAc= Ethylacetate, EtOH= Ethanol, DCM= Dichloromethane

The search for better, efficacious, safe and low-cost antileishmanials cannot be culminated into discovery of molecules that are exclusively leishmanicidal. Instead, focal point of antileishmanial drug discovery is to search for potent antileishmanial compounds, which are also auxiliary immunomodulatory. Since, *Leishmania* parasites romp with host immunity to establish intracellular parasitism, a quintessential leishmanicidal drug should be able to modulate host immune response for complete parasite clearance and avoid relapse. In recent times, the quest for immunomodulatory antileishmanial preparations or drugs has expanded manifolds and plenty of such natural compounds have been identified. Quassin from *Quassia amara* had been reported to enhance NOS II expression along with upregulation of



TNF- $\alpha$  and IL-12p70 and downregulation of TGF- $\beta$  and IL-10 [131]. 18 $\beta$ -Glycyrrhetic acid, a natural immunomodulator from *Glycyrrhiza glabra* induced p38 kinase mediated expression of NF- $\kappa$ B, NO and Th1 cytokines [132]. Picroliv, another natural immunomodulator from *Picrorhiza kurroa* enhanced the antileishmanial efficacy of a cocktail mixture of known antileishmanial drugs (Picroliv+Fluconazole+Miltefosine) in *L. donovani* infected hamsters [133]. Aminoglucosyl glycerolipid and cerebroside from *Desmodium gangeticum* [134] as well as Skimmianine from *Spiranthera odoratissima* [135] are known to induce NO-mediated killing of *Leishmania* parasites. Galactomannan from *Mimosa scabrella* enhanced production of NO and pro-inflammatory cytokines such as IL-1 $\beta$  and IL-6 [136]. Similar activity was evidenced in artemisinin treated *L. donovani* infected mice where artemisinin enhanced NO and declined IL-10 production [137]. *Bungarus caeruleus* snake venom, niranthin, isolated from *Phyllanthus amarus* and Berberine (*Berberis* spp.) are also demonstrated to polarize the immune environment from Th2 to Th1 type [138,45,139]. Macedo et al. [140] prepared polylactic-glycolic acid (PLGA) nanoparticles encapsulated with Crotonamine isolated from snake *Crotalus durissus terrificus* and observed that this preparation was Th1 stimulatory in nature.

## 5. Challenges and Future Prospectives

The search for substitute antileishmanial drugs has been pursued since decades and despite abundant literature, knowledge and research, we are yet to claim a commercially available drug based on natural molecules. However, the scenario can be improved by widely adopting standard procedures such as use of high throughput screening assays to monitor a multitude of compounds for obtaining definitive promising leads. Target-specific studies should be designed using reliable bioinformatics tools along with hybridization of synthetic chemistry so that scaffolding of natural molecules can yield better-suited candidate antileishmanial drugs.

In totality, clinically wide spectra associated with leishmaniasis have allowed its global manifestation with the frightful disease claiming mortality in thousands and morbidity in millions. Labelled as a disease of 'poor', leishmaniasis has failed to attract lucrative funding until recently, and thus the development of putative leads has been laggard. In this article, we summarized compounds/fractions from natural sources bearing promising antileishmanial potential. 'Naturo-medicines' as they can be appropriately called carry enormous potential for development of efficacious and safe future drugs at the time when present-day antileishmanial chemotherapy is becoming progressively blunt due to emerging drug-resistance and toxicity.

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